Crossing therapeutic boundaries: An immunotherapeutic simultaneously targeting Amyloid β, Tau, and α-synuclein amyloid aggregates

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Neurodegenerative diseases disregard biological boundaries, with multiple proteins aggregating to drive pathologies such as Alzheimer's disease (AD) and Parkinson's disease (PD). To meaningfully alter disease progression, new approaches must transcend these therapeutic boundaries. Yet most immunotherapy strategies remain focused on single proteins. Recent clinical efforts are now combining anti-Aβ and anti-Tau antibodies, hinting at a growing shift toward multi-target approaches. Here, we present Amyl-2, a rationally engineered protein that integrates multi-target recognition into a single molecule.

Objectives: Amyl-2 is generated by fusing a human IgG Fc domain with a proprietary conformational amyloid-binding domain. This modular design confers dual functionality: (i) selective recognition of aggregated conformers of $A\beta_{1\text{-}42}$, Tau, and α-synuclein, and (ii) phagocytic clearance of amyloid aggregates.

Methods: Binding affinity (SPR), aggregation inhibition (fluorescence spectroscopy), immunogold (electron microscopy), and human iPSC microglial phagocytosis (fluorescence microscopy) were assessed. Target engagement was tested in AD/PD mouse models and human brain tissues. Lecanemab, Etalanetug, and Prasinezumab biosimilars served as benchmarks.

Results: Amyl-2 has nanomolar affinity for amyloid aggregates, inhibits aggregation across Aβ, Tau, and α-synuclein, and promotes robust phagocytic clearance of amyloid aggregates. Amyl-2 effectively blocked Tau seeding in primary mouse neurons using AD patient-seeds with strong *ex vivo* binding to amyloid deposits in AD and PD mouse models and human patient tissues. Amyl-2 has a favorable PK and low immunogenicity profile. Amyl-2 shows no off-target binding across >6000 human proteins and in human tissue cross-reactivity assays.

Conclusions: Amyl-2 presents a strong potential to act as a disease-modifying therapeutic across amyloid-driven neurodegenerative diseases. Ongoing optimization to enhance binding affinities, improve brain permeability and mitigate amyloid-related imaging abnormalities (ARIA) strengthens the translational promise of this platform technology for AD, PD, and other amyloid-mediated diseases.